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- (iii) the compound that induces cleavage as recited in claim 13; and optionally;
 - (iv) an inhibitor of said compound of (iii); and optionally
 - (v) suitable buffer solutions.
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Please add the following new claim

c7

26. A method for identification of an inhibitor of amyloid-like fibrils or protein aggregate formation comprising the method according to claim 13 wherein the material of the sample is incubated in the presence and in the absence of the suspected inhibitor and the absence or the reduction of the detection of fibrils or protein aggregates in the material of sample incubated in the presence of the inhibitor in step (b) is indicative of the efficiency of the inhibitor.

REMARKS

Claims 1, 6, 9, 13, 20, 21, 24 and 25 have been amended. Claims 1-25 are pending. Claim 26 has been added. No new matter has been added.

Interview with Examiner Gabel

Applicants express thanks to Examiner Gabel for her courtesy in granting and conducting a telephone Interview with Applicants' representative on March 31, 2003. In the Interview, issues relating to the rejections in view of 35 U.S.C. §112, and §102, were discussed. In response to the §112 rejections, the claims were amended as discussed in the interview. Additionally, claim 20 was amended to add the generic language for Triton X 100 as discussed. The details of the discussions relating to §102 are provided below.

Rejection of Claims Under 35 U.S.C. 112, second paragraph

Claims 1-25 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

Claim 1 has been rejected as being vague and indefinite because it is unclear how the term "material" is used in the claim and how it relates to the terms in the preamble. Applicants have amended claim 1 in order to overcome the rejection. Claim 1 was amended to introduce the terms "in a sample" and "which has been previously treated with detergent or urea does solubilize the sample." The addition of such language should be sufficient to overcome the rejection

because it clarifies the relationship between the term “material” and other components of the claim.

Claim 1 has also been rejected as being indefinite because of the recitation of “contacting the filter with a sample”. Applicants traverse the rejection because the term “filter” is known in the art of biochemistry and molecular biology. It is known that a filter can be used in these arts as a means for the filtration of a solution, suspension, or emulsion or also in the context of immobilization of e.g. nucleic acid molecules or polypeptides. For example, filter membranes are used in DNA hybridization methodologies as well as the detection of proteins or polypeptides on filter membranes using dot blots or Western blotting. Thus, the term “filter” as used in claim 1 is clear to the person skilled in the art.

Claim 6 has been rejected because the term “material” is used inconsistently in the claims. Claim 6 has been amended to overcome the rejection. The amendment of claim 6 finds support in the description as originally filed on page 5, first paragraph.

Claims 8, 9 and 12 have been rejected as being vague and indefinite because of the recitation of the terms “material of the sample”. The term is rejected because it was used inconsistently in the claims. As described above, Applicants have amended claim 6 to remove the term “material”. Thus, any inconsistency has been corrected. It is now clear that the term “material” refers to a material of the sample. Claim 9 was also rejected as being confusing in view of claim 1. Additionally, claim 9 has been amended to further clarify the terms that have been objected to. Additionally, a “dot blot filter retardation assay is described in detail in example 8 within the specification.

Claim 10 has been rejected as being vague and indefinite because it is unclear how detection is effected by antibody peptide, enzyme, or chemical agent in the absence of a label or a signal producing system. Applicants disagree. It is not necessary for the antibody, peptide, enzyme, or chemical agent to carry a label in order to accomplish the detection. For instance, detection may be accomplished by using a second agent such as an antibody or peptide which specifically detects the first antibody, peptide, or polypeptide. The use of a second agent for detection is well known to those with skill in the art and also is described in the specification, i.e., Example 2, pages 18-19, and Example 8, pages 30-31. Additionally, an enzyme or chemical agent can be subjected to reaction conditions in order for detection. Use of a label would not be appropriate with these systems. These are all routine detection agents used in the art.

Claim 13 has been rejected as being indefinite because it is unclear how the “fusion protein” relates structurally and functionally to the “material of a sample. Claim 13 has been amended to explicitly recite the structural and functional relationship between the fusion protein and the material of a sample.

Claim 21 has been rejected as being vague and indefinite because of the recitation of the term “inhibitor”. New claim 26 has been added and claim 21 has been amended to depend from new claim 26. It is believed that this amendment should clarify the term “inhibitor”.

Claims 24 and 25 have been rejected as being indefinite because of several terms in the claims and because of the dependencies of the claims. Applicants have amended claims 24 and 25 to overcome the rejection.

Rejection of claims 1-3, 5-12, and 18-19 under 35 U.S.C. §102(b)

Claims 1-3, 5-12, and 18-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by Tateishi et al. for reasons of record. The Examiner has rejected prior arguments distinguishing the claims over Tateishi. Applicants previously argued that the sarkosyl treated material of Tateishi produced solubilization of the active component, causing it to pass through the filter membrane rather than being captured on the filter. In response to Applicants arguments, the Examiner has stated that claim 1 only recites that the filter is contacted with the sample and a detection step for determining whether the fibrils or aggregates are retained on the filter. The claim did not include an active filtering step.

Amended claim 1 is not anticipated by Tateishi. Claim 1 has been amended to clarify that the sample is treated with detergent or urea and that the ~~insoluble~~ amyloid-like fibrils or protein aggregates are filtered out. In contrast, Tateishi describes use of a surfactant, sarkosyl, to solubilize the causative agent of CJD. Tateishi then passes the solubilized component through a filter. In the instant claimed invention the causative agent of CJD is rendered insoluble with detergent or urea and in Tateishi it is rendered soluble with sarkosyl. Amended claim 1 cannot be anticipated by Tateishi because in amended claim 1 detergent or urea insoluble amyloid like fibrils or protein aggregates present in the sample are retained on the filter.

Tateishi described the following experiment in detail:

The supernatant of centrifuge homogenates obtained from the mouse brains infected with CJD was filtered through a membrane. In a subsequent step, the capacity of the filtrate to infect mice with CJD has been tested. It was demonstrated that the infective capacity of the filtrate was dependent on the mean size of the pores of the membrane used for the filtration. The experiment

led to the conclusion that the use of membranes with large pores results in filtrates with higher infective capacity than the use of membranes with small pores. This was interpreted as a result of the feature of the membrane with small mean size of the pores to retard the causative agent of CJD. Further, it has been demonstrated that the infective capacity of the filtrate may be increased by the detergent sarkosyl since said detergent solubilized the causative agent of CJD and thus favored the passage of said agent of membranes with small mean size of the pores. Consequently, Tateishi et al. demonstrates that due to the use of the detergent, the amount of "causative agent of CJD" which is retarded by the membrane is quantitatively reduced. The described experiment clearly shows that the removal of the causative agent of CJD through the membrane filtration method is prevented by the previous incubation of the sample with the detergent sarkosyl.

In contrast, the present invention is based at least in part upon the experiment described in the present application demonstrating that polyglutamin aggregates are filtered out by a membrane. Additionally, the polyglutamin were found to be insoluble in detergents or urea. As the aggregates can be selectively concentrated by pre-treatment with detergent or urea and removal of detergent or urea soluble parts of the sample.

Tateishi et al. neither teach nor suggest the use of detergent or urea for the solubilization of material of a sample comprising the protein aggregates recited in the claimed invention. Furthermore, Tateishi et al. does not teach the filtration of a material of a sample previously treated with detergent or urea to solubilize the sample and to concentrate the detergent and urea in soluble aggregates on a filter.

Rejection of claims 4 and 17 under 35 U.S.C. §103

Claims 4 and 17 have been rejected under 35 U.S.C. §103 as being unpatentable over Tateishi et al. in view of Trottier and further in view of Stott et al. The Examiner maintains that Tateishi et al. as discussed previously combined with Trottier et al. and Stott et al. would render the invention obvious. The Examiner maintains that Trottier et al. teach neurodegenerative diseases such as Huntington's, and that these diseases are associated with polyglutamin expansion. Trottier et al. further characterize antibodies that recognize these polyglutamin expansions and use them to detect the presence of the expansions on Western Blot. Further, the Examiner maintains that Stott et al. teach polyglutamin repeats and that their abnormal expansion is linked to neurodegenerative diseases. It was concluded that one of ordinary skill in the art

would have had reasonable expectation of success of detecting proteins with polyglutamin expansion in view of Trottier et al. and Stott et al. using the method and device of Tateishi et al.

The claimed invention would not have been obvious in view of the combination of references because the combination does not produce the claimed invention. As argued previously, the Tateishi et al. teachings do not provide for a method for detection of insoluble fibrils and protein aggregates. Therefore, the teaching of Tateishi et al. alone or in combination with these references would not have made the present invention obvious.

Rejection of Claims 13-14, 16 and 20 Under 35 U.S.C. 103(a)

The Examiner maintains that claims 13-14, 16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al. in view of Smith and Stott et al. Smith discloses a fusion protein which comprises an amyloidogenic polypeptide and a polypeptide that enhances solubility or prevents aggregation. Therefore, the Examiner maintains that the combination of Tateishi et al., Smith and Stott et al. would make these claims obvious. The claimed invention would not have been obvious in view of the combination of references because the combination does not produce the claimed invention. As argued previously, Tateishi et al. does not describe or suggest a method of detecting the presence of detergent- or urea-insoluble fibrils or protein aggregates on a filter. Further, the combination of Tateishi et al., Smith and Stott et al. do not provide any additional teaching that would provide guidance for the person skilled in the art to develop the methods of the invention.

Rejection of Claims 15 and 21-25 Under 35 U.S.C. 103(a)

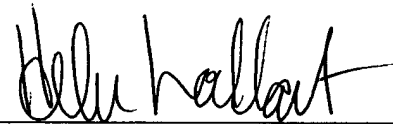
The Examiner has also rejected claims 15 and 21-25 under 35 U.S.C. 103(a) as being unpatentable over Tateishi et al. in view of Smith and Stott et al. and further in view of Vitek et al. (US 2,935,927). The Examiner maintains that Vitek et al. further discloses advanced glycosylation end-products – amyloid polypeptides that facilitate aggregation of fibrils in neurodegenerative diseases. The Examiner also maintains that treatment of such diseases with compositions comprising inhibitors are further disclosed. Therefore, the Examiner concludes that one of skill in the art would have been motivated to inhibit formation of amyloid fibrils using inhibitors in the form of pharmaceutical compositions. Claims 15 and 21-25 were not obvious for at least the same reasons as discussed above. The methods of the invention are directed to an *in vitro* method comprising contacting a filter with material of a sample suspected to contain fibrils or aggregates that are detergent- or urea-insoluble. Tateishi et al., as argued

previously, does not provide for a method of detecting insoluble fibrils or proteins, and the combination of references does not provide additional guidance that would make obvious the rejected claims.

SUMMARY

It is believed that all of the pending claims are now allowable. If the Examiner has any questions or comments, she is encouraged to contact Applicants' representative at the number listed below.

Respectfully submitted,

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MARKED-UP CLAIMS

1. (Amended) A method of detecting the presence of detergent- or urea-insoluble amyloid-like fibrils or protein aggregates in a sample on a filter comprising the following steps:

(a) contacting said filter with [material of] a sample suspected to comprise said fibrils or aggregates which has been previously treated with detergent or urea to solubilize the sample and filtering said sample to capture said detergent or urea insoluble amyloid-like fibrils or protein aggregates; and

(b) detecting whether said fibrils or aggregates are retained on said filter.

6. (Amended) The method of any one of claims 1 to 3 wherein said filter [is comprised of material with] has a low capacity for protein adsorption. *Support?*

9. (Amended) The method of any one of claims 1 to 3 and 7 wherein detergent- or urea-soluble material of the sample is simultaneously with or subsequent to the contacting of said filter with material of the sample in step (a), sucked through said filter.

13. (Amended) The method of any one of claims 1 to 3 and 7 wherein said material of the sample comprises a fusion protein comprising a peptide or polypeptide that enhances solubility or prevents aggregation of said fusion protein, an amyloidogenic peptide or polypeptide that has the ability to self-assemble into amyloid-like fibrils or protein aggregates when released from said fusion protein and a cleavable site that separates the above-mentioned components of the fusion protein further comprising the following steps prior to step (a):

(a') incubating [a] said fusion protein [comprising a peptide or polypeptide that enhances solubility or prevents aggregation of said fusion protein, an amyloidogenic peptide or polypeptide that has the ability to self-assemble into amyloid-like fibrils or protein aggregates when released from said fusion protein and a cleavable site that separates the above-mentioned components of the fusion protein] in the presence of a suspected inhibitor of amyloid-like fibril or protein aggregate formation; and

(a'') simultaneously with or after step (a'), further incubating with a compound that induces cleavage at said cleavage site.

20. (Amended) The method of any one of claims 1 to 3, and 7 wherein said detergent is Sodium Dodecyl Sulphate (SDS) or t-octylphenoxypolyethoxyethanol (TRITON X-100TM).

21. (Amended) An inhibitor of amyloid-like fibril or protein aggregate formation identified by the method of claim [14] 26.

24. (Amended) A diagnostic composition comprising

(i) the fusion protein [of any one of the preceding claims] as recited in claim 13.

25. (Amended) The diagnostic composition of claim 24 further comprising

(ii) the filter for filtering the fusion protein as recited in claim 1 [of any one of the preceding claims] optionally or preferably contained in a microtiter plate; and optionally

(iii) the compound that induces cleavage [of any one of the preceding claims] as recited in claim 13; and optionally;

(iv) an inhibitor of said compound of (iii); and optionally

(vi) suitable buffer solutions.

New Claim 26:

26. A method for identification of an inhibitor of amyloid-like fibrils or protein aggregate formation comprising the method according to claim 13 wherein the material of the sample is incubated in the presence and in the absence of the suspected inhibitor and the absence or the reduction of the detection of fibrils or protein aggregates in the material of sample incubated in the presence of the inhibitor in step (b) is indicative of the efficiency of the inhibitor.